EXHIBIT E

RESPONSE TO REPORT ENTITLED,"*BRAIN CANCER CLUSTER, MCCULLOM LAKE VILLAGE AND SURROUNDING AREA, MCHENRY COUNTY, ILLINOIS*"

Dated October 15, 2007
by
Richard Neugebauer, M.P.H., Ph.D.

In the case of

Gates et al., v. Modine Manufacturing Co. et al.

Submitted by

Patricia A. Buffler, M.P.H., Ph.D.

January 26, 2007

INTRODUCTION

I am a Professor of Epidemiology at the School of Public Health, University of California, Berkeley, where I also served as Dean from 1991 to 1998. I have a concurrent appointment as an Adjunct Professor in the Department of Epidemiology and Biostatistics at the University of California San Francisco, School of Medicine (see Exhibit A). I have been retained by the defendents in this matter.

This document comments on the expert report of Richard Neugebauer, MPH, PhD, and on information given by Dr. Neugebauer at his deposition (November 21, 2006), in the case of Gates et al. v. Modine Manufacturing Co. et al. Specifically, I critique the epidemiologic methods used by Dr. Neugebauer to evaluate the incidence of oligodendroglioma among residents of McCullom Lake Village and the surrounding area in McHenry County, Illinois; his assessment of the available literature on the epidemiology of vinyl chloride monomer (VCM) and brain cancer; the conclusions reached by Dr. Neugebauer based on his preliminary evaluation; and his plans for further epidemiologic investigation of this issue.

In forming my opinions in this case, which I list below, I have relied on my education, my experience in teaching epidemiology, my experience in planning, conducting and interpreting epidemiologic and other studies of numerous environmental exposures and cancer sites; my knowledge of generally accepted epidemiologic methods; and review of numerous published scientific articles pertaining to the VCM and the cancers of interest in this case. The papers that I reviewed are discussed and listed in the attached list of references.

OPINIONS

It is my opinion that Dr. Neugebauer's evaluation of the incidence of brain cancer among residents of McCullom Lake Village and the surrounding area is not valid and does not provide support for the idea that environmental contamination from industrial operations in the area has caused an excess of oligodendroglioma or any form of brain cancer. There are several reasons for this opinion.

1. Dr. Neugebauer's report does not provide a clear basis for specifying the target population used in his preliminary investigation of observed and expected numbers of oligodendrogliomas. Although he states that monitoring data on industrial contaminants and data on the flow of groundwater support the choice of a target population "within a three mile radius south of Ringwood," his analysis includes people living west, not south, of the alleged industrial sources of contamination. His report also does not indicate the time of potential exposure, and, thus, his focus on cases occurring in 2002-2005 is not adequately justified.

2. Dr. Neugebauer claims that ".the rates of two brain cancer subtypes, glioblastoma...and oligodendroglioma..., appear considerably elevated in this small geographic area." In his report Dr. Neugebauer does not present any data

to substantiate his claim with regard to glioblastoma. The only two cases of glioblastoma who lived in the target area at the time of diagnosis were diagnosed in 2006. And, his analysis of observed and expected numbers of oligodendrogliomas is not valid because he included, as an observed case, one person who worked in, but did not live in, the area, whereas he did not count in the target population used for computing expected numbers the people who worked, but did not live, in the area. If this one case is excluded from the analysis, the difference between the observed and the expected number of oligodendrogliomas is no longer statistically significant. In addition, one other observed case lived west, not south, of the alleged sources of groundwater contamination, and the inclusion of this case, as well as the inclusion of the general population living west of the industrial sources, may not be warranted.

Finally, Dr. Neugebauer's investigation of observed and expected numbers of oligodendrogliomas did not adjust for age, gender or any other demographic factor typically consiered in such ecologic analyses. Even if his ecologic analysis had been done using optimal methods, this type of analysis would not be adequate to support a conclusion about a causal relation between exposure to groundwater contaminants and oligodendroglioma. Such a conclusion would require an investigation of individual-level exposure, as well as other supporting evidence, such as replication of findings in another population with similar environmental exposures

3. Dr. Neugebauer's review of the scientific literature pertaining to VCM, the agent for which he claims there is "evidence of a link with brain cancer" (deposition exhibit 2A, page 2, paragraph 1), is incomplete and ignores important recent studies of VCM and brain cancer. Based on the complete body of current literature, there is no consensus among scientists, nor is it generally accepted, that VCM is an established cause of any form of brain cancer in humans.

It is also my opinion that Dr. Neugebauer's plans for the design, analysis and interpretation of a "full" investigation of brain cancer incidence in the geographic area of interest are vague in many important respects. The planned investigation, like the preliminary investigation, is ecologic in nature and will not, therefore, determine if there is a causal relation between exposure to contaminants of air or groundwater and brain cancer.

QUALIFICATIONS AND OTHER DISCLOSURE INFORMATION

A. BACKGROUND, EXPERIENCE AND EXPERTISE

I began my career in Public Health in 1960 as a Public Health Nurse in Central Harlem, New York City and Alameda County, California, and returned to graduate school in 1963 for studies in epidemiology at the University of California, Berkeley. I received a Ph.D.

in epidemiology (1973) and a Master of Public Health degree in Epidemiology and Public Health Administration (1965) from that institution.

Since 1980 I have maintained a large research program with approximately $2 million/annually of peer-reviewed research funding. I have been Principal Investigator for numerous epidemiologic studies, many involving exposure assessment and the assessment of environmental hazards. While I was on the faculty of the University of Texas Health Science Center School of Public Health in Houston (1979-1991) my research focused on the study of cancer among workers and residents of the Texas-Louisiana Gulf Coast Area and the possible associations with employment in the petrochemical and petroleum refining industries and residence in communities adjacent to these facilities. During this time I served as Director of the Southwest Center for Occupational Safety and Health and conducted several studies of cancer including liver cancer, lung cancer, laryngeal cancer, brain cancer and leukemia which addressed the contribution of chemicals to cancer risk in humans. I am currently conducting a large population-based case-control study of childhood leukemia in Northern California which seeks to identify the association of chemical exposures with genetic changes which may then lead to leukemia in children. This research focuses on the molecular and environmental epidemiology of cancers in children and more broadly on the genetic and environmental epidemiology of cancer.

In addition to designing and conducting epidemiologic studies, I teach other scientists how to conduct and evaluate epidemiologic studies. At the University of California School of Public Health I annually offer a course in the epidemiology of cancer for graduate students and assist with the teaching of courses such as the Introduction to Epidemiology, Epidemiologic Methods and Seminars in Ethics in Epidemiologic Research and Epidemiologic Research Topics in the Division of Epidemiology, and other school-wide courses such as Ethics in Public Health Research and Practice, Leadership in Public Health and Doctoral Seminar in Public Health. In addition, I currently serve as the faculty advisor and mentor to nine doctoral students in epidemiology and numerous master's degree students in epidemiology and biostatistics. My Curriculum Vitae, which is attached hereto as Exhibit A, delineates my extensive experience as an epidemiologist.

I have served as President for the International Society for Environmental Epidemiology, the American College of Epidemiology, the Society for Epidemiologic Research and the Chair of Epidemiology Section of the American Public Health Association. I am a member of numerous scientific societies, including but not limited to the Society for Epidemiologic Research (since 1970); the American Epidemiological Society (elected to membership in 1981); the American College of Epidemiology (Fellow-elected 1982); International Epidemiologic Association (since 1979); the American Society for Preventive Oncology (Founding member-1976); the American Association for Cancer Research (since 2002), the International Council for Occupational Health (since 1979); the International Society for Environmental Epidemiology (Founding Member - 1987); and the International Society for Exposure Assessment (Charter member-1990). In 1993 I was elected as a Fellow of the American Association for the Advancement of Science in recognition of my contributions in environmental epidemiology (Secretary, Medical

Sciences Section 1994-1999). In 1994, I was elected to membership of the Institute of Medicine/National Academy of Sciences. In 2005, I was elected to the Council of the International Association of Epidemiology as the representative for North America, and I was appointed to the National Board of Public Health Examiners.

I have received appointments to and served on committees and Boards for the following groups, among others: National Research Council, World Health Organization, U.S. Environmental Protection Agency (USEPA), the former U.S. Congress Office of Technology Assessment, National Institutes of Health, Centers for Disease Control, Agency for Toxic Substances and Disease Registry, National Superfund Commission, Electric Power Research Institute, Food and Drug Administration, U.S. Department of Defense, U.S. Department of Energy, the U.S.-Japan Radiation Effects Research Foundation, the Lovelace Respiratory Research Institute, the National Urban Air Toxics Research Institute and the FMC Corporation. Exhibit A to my declaration contains a full list of my appointments and committee memberships.

I serve or have served on the Editorial Board for the American Journal of Epidemiology, the Journal of Occupational and Environmental Medicine, Environmental Health Perspectives, Annals of Epidemiology and Neuro-oncology, and regularly serve as a peer reviewer for these and numerous other well established and prestigious journals.

B. DEPOSITION AND TRIAL TESTIMONY

Baxter Healthcare Corp. v. Joan E. Denton, Ph.D. and California Office of Environmental Health Hazard Assessment
Superior Court of California, County of Sacramento, No. 99 CS 00868.
Testimony May 2002.
Akin Gump Strauss Hauer and Feld

Hernandez v Fairchild, IBM
Superior Court of California, County of Santa Clara
Deposition 2003, Trial 2004
Jones Day

Redlands Tort Litigation
Superior Court of California
Deposition 2004
Gibson Dunn and Crutcher

Moss v Venaco
Superior Court of California, County of Los Angeles Central District
Deposition July 2006
Latham and Watkins

Adams v Cooper Industries
US District Court, Eastern District of Kentucky at Lexington
Deposition November 2006
Crowell Moring

C. CONSULTATION AND PROFESSIONAL FEES

My hourly fee for time committed to deposition and trial testimony is $700/hour and $600/hour for review and preparation of materials.

EXPERT REPORT OF DR. RICHARD NEUGEBAUER

Introduction

Dr. Neugebauer's original report entitled "Brain Cancer Cluster, McCullom Lake Village and Surrounding Area, McHenry County, Illinois" was dated October 15, 2006, and was modified in his deposition of November 21, 2006. Most of my comments pertain to the version of the report that was submitted to the Court as exhibit D to the Plaintiffs' motion for class certification (labeled exhibit 2A of the deposition).

In his report, Dr. Neugebauer claims that the information available to him "concerning diagnosed cases of brain cancer among residents of McCullom Lake Village and in the surrounding area of McHenry County Illinois, is sufficient to raise substantial public health concerns and to warrant a full epidemiologic investigation of a possible cancer cluster in the area" (deposition exhibit 2A, page 1, paragraph 3). He summarizes the preliminary assessment that prompted this conclusion, and he outlines his plans for further investigation.

Dr. Neugebauer's Preliminary Assessment

This section summarizes and comments on Dr. Neugebauer's preliminary assessment of brain cancer incidence among residents of McCullom Lake Village. This assessment provided the basis for his conclusions.

Summary

Dr. Neugebauer asserts that "...McCullom Lake Village lies close to a major source of environmental contamination..." (deposition exhibit 2A, page 1, paragraph 4). He notes that EPA environmental sampling reports indicate that volatile organic compounds (VOCs) were released into groundwater by two industrial operations near this area, that the VOCs included trichloroethylene, which can be degraded into vinyl chloride, a established carcinogen for which there is "evidence of a link with brain cancer" (deposition exhibit 2A, page 2, paragraph 1). He cites a report prepared by STS consultants and submitted to the Illinois EPA (deposition exhibit 19) that claims a southward direction of deep groundwater flow from the area of the Modine industrial site and the Rohm and Haas Plant, as well as an EPA report (deposition exhibit 20) that

classified people living within a three mile radius of the Morton plant as "'the target population potentially affected by groundwater contamination'" and "the population living within a five mile radius of the plant was considered at risk through inhalation" (deposition exhibit 2A, page 2, paragraph 2).

Dr. Neugebauer further asserts that "...the rates of two brain cancer subtypes, glioblastoma...and oligodendroglioma..., appear considerably elevated in this small geographic area" (deposition exhibit 2A, page 1, paragraph 4). His report identifies five people with oligodendroglioma, diagnosed during the time period 2002 through 2005, who, at diagnosis, lived in "the geographic area of concern", had previously lived in this area or had worked in the area. Among these five cases, "3 lived or worked within the 3 mile radius south of Ringwood" (deposition exhibit 2A, page 3, paragraph 1). He claims that the population of the geographic area was 18,800 (in each year of the four-year period), and he uses a "SEER/CBTRUS" oligodendroglioma rate for the period 1998-2002 (0.5 per 100,000 population) to calculate an expected number of 0.38 for oligodendroglioma. He concludes that the rate of oligodendroglioma in the exposed population is 7.9 times that of the rate in the general population, a result that he says is statistically significant. The report concludes that this analysis "...suggests that the rate of oligodendroglioma is substantially and significantly increased in the target population lying within a 3 mile radius south of Ringwood, McHenry County, an area that includes McCullom Lake Village" (deposition exhibit 2A, page 3, paragraph 2)

During the deposition, a revised report marked as exhibit 2 was produced. However, the plaintiffs' counsel objected to the revised report, as it had not been submitted to the Court or reviewed by plaintiffs' counsel (deposition, page 39). The revised report is not discussed further here.

Comments

The basis for specifying a target population of individuals likely to have consumed contaminated drinking water or likely to have been exposed to industrial emissions via inhalation is unclear. Dr. Neugebauer does not indicate the time of potential exposure or the precise geographic boundaries of potential exposure. The EPA report that he cites refers to a three-mile or five-mile radius around the industrial facilities, whereas Dr. Neugebauer's preliminary analysis of observed and expected numbers of cases appears to consider only the geographic area three miles south of the industrial facilities, i.e., the "target population lying within a 3 mile radius south of Ringwood, McHenry County, an area that includes McCullom Lake Village" (deposition exhibit 2A, page 3, paragraph 1). Dr. Neugebauer's citations of the epidemiologic literature on VCM and brain cancer are incomplete and did not include important recent studies with longer follow-up, larger study populations and better exposure estimation. These studies raised substantial doubts about the relation between VCM exposure and brain cancer, as indicated by the research summarized later in the present report. In addition, one of the papers (deposition exhibit 8) that he cited in his references is an advocacy commentary, rather than scientific review paper; some aspects of this paper have been rebutted (Price, 2005). In his preliminary analysis, Dr. Neugebauer includes as an observed case of oligodendroglioma

a resident of Wonder Lake, an area west, not south, of the industrial facilities (see Neugebauer transcript and Exhibits 28-37; 42-44).

Dr. Neugebauer's report does not adequately support his focus on the 2002-2005 time period. The report does not specify the basis for the assertion that the target population consisted of 18,800 people annually, nor does the report indicate that he estimated the size of the population that spent time working in this area. The three observed cases include one person who spent some time in the area as part of his job as a vehicle patrolman but did not live in the area (see attached table). If this case is excluded from the analysis, the difference between the observed number (N=2) and the expected number (N=0.38) of oligodendrogliomas is not statistically significant. The number of observed oligodendrogliomas would be reduced to only one if the case who moved to Wonder Lake (west of the industrial facilities) seven years before diagnosis were also removed. This case would be ineligible due to lack of exposure, if it is presumed, as done by Dr. Neugebauer, that the groundwater flows in a southerly, rather than westerly, direction.

Dr. Neugebauer's analysis does not adjust for age, gender or race or any other factor related to oligodendroglioma, and Dr. Neugebauer does not provide any basis for assuming that the population included in the SEER/CBTRUS registries is similar to the population in the target area with respect to determinants of oligodendroglioma. His conclusion, that the rate of oligodendroglioma in the "exposed" population is 7.9 times that of the rate in the general population, cannot be accepted as valid due to his inclusion as an observed case the person who worked in, but did not live in, the area (while not counting such people in the target population) and due to his failure to adjust for age and other factors.

The results of the preliminary analysis presented in Dr. Neugebauer's report appear to represent an extreme version of the "Texas sharpshooter" effect, produced by his failure to specify appropriate time and geographic population boundaries. This effect, described by Thun and Sinks (2004) (and others), occurs because "The fact that the boundaries of a suspected cluster are defined based on when and where the cases actually occurred increases the likelihood that random variation will appear to give rise to clusters."

Although Dr. Neugebauer's report claimed that "...the rates of two brain cancer subtypes, glioblastoma...and oligodendroglioma..., appear considerably elevated in this small geographic area" (deposition exhibit 2A, page 1, paragraph 4), the report did not provide any data to support this assertion with regard to glioblastoma. The only two cases of glioblastoma who lived in the target area at the time of diagnosis were diagnosed in 2006, a year after the specified period (2002-2005) of Dr. Neugebauer's analysis (see Neugebauer transcript and Exhibits 28-37; 42-44).

Dr. Neugebauer's Plans for Further Investigation

Summary

Dr. Neugebauer presents his plans for a full investigation of a possible cancer cluster (deposition exhibit 2A, page 2, in paragraphs 3 and 4). He asserts that such an investigation requires "data on the size of the exposed and unexposed populations" and data "on the number of cases of the brain cancer subtypes being investigated both in the exposed population and in the general population (the unexposed population)" (deposition exhibit 2A, page 2, paragraph 4). He further states that "we will compare the cancer rates in the exposed population to the rates in other Illinois communities that are similar to McCullom Lake Village and the surrounding area..." (deposition exhibit 2A, page 2, paragraph 4). He also notes that he will conclude that the cancer rate is elevated "when the observed number of cases is significantly greater than the expected number of cases, for example, 2 times greater" (deposition exhibit 2A, page 2, paragraph 3).

Comment

The purpose of Dr. Neugebauer's "full investigation" is to "...examine whether increased rates of specific brain cancer subtypes are associated with a known source of industrial contamination..." (deposition exhibit 2A, page 1, paragraph 3). A valid investigation to determine if there is a causal relation between exposure to industrial contaminants and brain cancer typically would require an individual-level study with exposure data for the individual cases, rather than the ecologic study proposed by Dr. Neugebauer using area-level exposure estimates (Thun and Sinks, 2004).

The plans for the design, analysis and interpretation of the full investigation are vague in many important respects. The plans do not specify the exposure(s) of interest or indicate how the exposed population will be defined and enumerated. There is no explanation of procedures that will be used to select Illinois communities that are "similar" (a term that also is not defined) to McCullom Lake Village. The time period of the planned study is not stated. The only data that Dr. Neugebauer appears to believe are "essential" are data on the size of the exposed and unexposed populations and the number of cases in each group (deposition exhibit 2A, page 2, paragraph 4), and his plans do not provide these numbers. It appears that, contrary to generally accepted epidemiologic practice, Dr. Neugebauer does not consider the distributions of the populations and cases by age or other factors to be relevant, despite the fact that the incidence of gliomas, which include glioblastoma and oligodendroglioma, is known to vary considerably by age, gender and race (Wrensch et al., 2002; Hess et al., 2004).

The choice of a twofold elevation in the cancer rate among the exposed compared to the unexposed population as a criterion for judging the significance of the results of the planned study (deposition exhibit 2A, page 2, paragraph 4) also is unconventional, arbitrary and not generally accepted by epidemiologists. This criterion ignores random variability in disease rates, an especially important consideration when examining variation in disease rates in small groups (Thun and Sinks, 2004).

EPIDEMIOLOGIC RESEARCH ON VCM AND BRAIN CANCER

Most epidemiologic research on the health effects of VCM has evaluated workers who produced or used VCM in a variety of industrial settings. In these studies, the route of exposure was inhalation, and many of the available studies included workers exposed to VCM concentrations up to thousands of ppm – orders of magnitude higher than concentrations that would characterize environmental exposure. No consensus among scientists that VCM causes brain cancer in humans has emerged from these studies. Although environmental exposure levels have not been established for people living in the communities referred to in Dr. Neugebauer's report, the extreme exposure levels in the early occupational studies, and the associations measured in the studies, are not directly applicable to low-level environmental exposures.

The Available Epidemiologic Studies

In the United States (US), a number of separate studies, published in the 1970s and 1980s, assessed mortality from cancer and other diseases among workers exposed to VCM (Lewis et al., 2003; Mundt et al., 2000; Wong et al., 1991; Waxweiler et al., 1981; Wu et al., 1989; Dahar et al., 1988; Buffler et al., 1979; Cooper, 1981; Ott et al., 1975; Tabershaw and Gaffey, 1974; Waxweiler et al., 1976; Monson et al., 1974; Monson et al., 1975). The cohorts of workers investigated in these studies were combined into a single US cohort consisting of 10,173 male workers from 37 plants (Wong et al., 1991), and the most recent publication from the study examined mortality from various cancers from 1942 through 1995 (Mundt et al., 2000).

In Europe, the epidemiologic research on VCM evolved in a similar way: a number of relatively small cohorts of workers in Italy, Norway, Sweden and the United Kingdom (Heldaas et al., 1984; Heldaas et al., 1987; Molina et al., 1981; Langard et al., 2000; Jones et al., 1988; Hagmar et al., 1990; Fox and Collier, 1977; Byren et al., 1976; Belli et al., 1987) were combined into a large, more informative cohort consisting of 12,706 male workers from 19 plants (Simonato et al., 1991). The European cohort study was updated recently to include mortality data for the time period 1955 through a date that varied from 1993 to 1997 depending on the plant; the study also examined cancer incidence during a similar time period among workers from 13 of the 19 study plants (i.e., plants in Norway, Sweden and the UK) (Ward et al., 2001).

In addition to the large, multi-center US and European studies, research has been done on smaller groups of workers exposed to VCM in France (Laplanche et al., 1992), Germany (Weber et al., 1981), Quebec Canada (Theriault and Allard, 1981), Japan (Nakamura, 1983), China (Huang, 1996, cited in Boffetta et al., 2003), Taiwan (Wong et al., 2002) and the Soviet Union (Smulevich et al., 1988). The French study (Laplanche et al., 1992) included 1,100 men exposed to VCM at 12 plants and 1,100 unexposed men from the same plants, individually matched to an exposed subject on plant, age and physician. These two groups of workers were observed from about 1980 through 1988. The German study (Weber et al., 1981) included 7,021 men potentially exposed to VCM in VCM or

polyvinyl chloride (PVC) production, 4,007 male PVC processing workers who would have had low or no exposure to VCM and a reference group of 4,910 male workers in the chemical industry who were unexposed to VCM. The subjects were observed from an unspecified starting date sometime before 1960 through 1974. The Canadian study (Theriault and Allard, 1981) included 451 men exposed to VCM and 870 unexposed men from the same company; these workers were observed from 1948 through 1977. The Japanese study (Nakamura, 1983) included 4,524 men who were employed at 25 plants that produced VCM or PVC and who were followed up from 1950 through 1975. The Chinese study (described by Boffetta et al., 2003) included 5,958 subjects from 14 plants observed from 1958 through 1981. The Taiwanese study consisted of 3,293 male VCM workers with follow-up from 1985 through 1997 (Wong et al., 2002). Cohort studies of other groups have not been updated since the 1980s. The study conducted in the Soviet Union (Smulevich et al., 1988) included 2,195 men and 1,037 women employed in VCM-exposed jobs at a VCM and PVC production facility and observed between 1939 and 1977.

Counting only the most recent reports of the US and European multi-center studies, the research on VCM consists of nine independent investigations (Ward et al., 2001; Mundt et al., 2000; Laplanche et al., 1992; Weber et al., 1981; Theriault and Allard, 1981; Nakamura, 1983; Huang, 1996; Wong et al., 2002; Smulevich et al., 1988). Of these, five reported observed and expected numbers of brain cancer deaths or cases (Ward et al., 2001; Mundt et al., 2000; Smulevich et al., 1988; Weber et al., 1981; Wong et al., 2002). There was no brain cancer death in the Canadian studies by Theriault and Allard (1981) or in the French study by Laplanche et al. (1992). There was one brain cancer death in the Chinese study by Huang et al. (1996), but the expected number apparently was not provided (Boffetta et al., 2003); and the Japanese study by Nakamura (1983) did not mention either the observed or the expected number of brain cancers. Several studies have reported histolopathologic information on the brain cancers observed among VCM-exposed workers (Tabershaw and Gaffey, 1974; Waxweiler et al., 1976; Cooper, 1981; Jones et al., 1988; Hagmar et al., 1990; Mundt et al., 2000).

In addition to analytic epidemiologic studies, reviews of the association between VCM and various forms of cancer have been published (for example, Doll, 1988; McLaughlin and Lipworth, 1999; Bosetti et al., 2003; Boffetta et al., 2003; IARC, 1987; USEPA, 1994). Two of these presented a meta-analysis of various cancers (Boffetta et al., 2003; Bosetti et al., 2003). Meta-analyses provide statistical summaries of the overall pattern of risk by combining the results of individual studies while weighting them appropriately for differences in study population sizes. In a letter to the editor, Swaen and Duijts (2005) also presented a meta-analysis of cancer mortality among workers exposed to VCM. The data used in the latter meta-analysis were the same as those used by Boffetta et al. (2003), and the results were similar. Thus, the present report does not discuss the results of Swaen and Duijts (2005) further.

Findings of the Available Research

VCM is a well-established cause of human angiosarcoma of the liver (IARC, 1987; USEPA, 1994). The occurrence of this rare form of cancer was due to very high inhalation exposures that occurred in industrial settings before the 1970s and has been associated in exposure-response analyses with high cumulative exposure and long duration of exposure to VCM. Some of the early epidemiologic studies reported positive statistical associations between occupational exposure to VCM and other forms of cancer, including brain cancer. In the 1980s, several scientists interpreted the available evidence as indicating that VCM caused brain cancer (IARC, 1987; Moss, 1985; Purchase et al., 1987; Infante, 1981). However, such a conclusion was controversial (Doll, 1988) and was based on limited evidence from early investigations that was weakened by later, larger and/or more in-depth studies (Mundt et al., 2000; Ward et al., 2001; Wu et al., 1989; Lewis et al., 2003; Boffetta et al., 2003; McLaughlin and Lipworth, 1999; Bosetti et al., 2003). Importantly, the results of the large, most recent US and European multi-center studies do not provide consistent support for a relation between VCM and brain cancer (Mundt et al., 2000; Ward et al., 2001). This inconsistency, along with other considerations discussed below, argues against a true causal relation.

The US cohort study (Mundt et al., 2000) found 36 observed compared to 25.3 expected brain cancer deaths, with a standardized mortality ratio (SMR) of 1.42 (95% CI=1.00-1.97). This result was of borderline statistical significance. Most importantly, in comparisons of longer term workers with shorter term workers, the rate ratio (RR, estimated as a hazards ratio; adjusted for age at first exposure and year of first exposure) did not increase with increasing duration of exposure (<5 years of exposure: RR=1.0; 5-9 years: RR=2.0, 95% CI=0.9-4.7; 10-19 years: RR=0.7, 95% CI=0.2-2.0; 20+ years: RR=1.9, 95% CI=0.8-5.0). The lack of evidence of an exposure-response trend weighs against a causal interpretation of the weak statistical association. Demonstration of an exposure-response trend is an important consideration in reaching the conclusion that a statistical association is causal (Hill, 1965).

The excess of brain cancer reported by Mundt et al. (2000), when examined in more detail (Lewis et al., 2003; Lewis and Rempala, 2003), was found to have been concentrated in only one plant, and there was no exposure-response relationship with VCM. These findings suggest that the excess was not due to VCM. Lewis et al. (2003) demonstrated that most of the increase in brain cancer mortality was due to an excess at a single US plant, ie, the Louisville plant (15 observed compared to 6.5 expected, SMR=2.29, statistically significant), whereas for all other 36 plants combined, observed and expected numbers of brain cancer deaths were similar (21 observed compared to 18.8 expected, SMR=1.12, not statistically significant). In contrast, the SMR for liver and biliary cancer deaths was elevated both at the Louisville plant (24 observed and 6 expected, SMR=400, statistically significant) and at the other 36 plants (56 observed and 16.3 expected, SMR=344, statistically significant). This lack of internal consistency for brain cancers, like the absence of a demonstrable trend of increasing RRs with increasing duration of exposure, also weighs against a causal interpretation of the statistical association seen in the overall cohort. Furthermore, a case-cohort study of the relation

between exposure to VCM and brain cancer, conducted at the Louisville plant, where the excess of brain cancer mortality was concentrated, reported a strong exposure-response relation between VCM and angiosarcoma of the liver but no association between VCM exposure and brain cancer (Lewis and Rempala, 2003), a set of results that precludes a conclusion that the excess of brain cancer at the plant was caused by VCM. An earlier case-control study, conducted at the same plant, also found no association between estimated exposure to VCM and brain cancer (Wu et al., 1989).

The multi-center European cohort study (Ward et al., 2001) reported a clear excess of liver cancer mortality (53 observed, SMR=2.40, 95% CI=1.80-3.14) and incidence (29 observed, standardized incidence ratio (SIR)=3.98, 95% CI=2.67-5.72) but no excess of brain cancer, based on 24 observed compared to 25.8 expected deaths (SMR=0.93, 95% CI=0.60-1.39) and 19 observed compared to 20.9 incident cases (SIR=0.91, 95% CI=0.55-1.42). There was no clear exposure-response relationship for brain cancer (<35 ppm-years: RR=1.0; 35-99 ppm-years: RR=1.37, 95% CI=0.28-6.82; 100-535 ppm-years: RR=3.45, 95% CI=0.94-12.6; 536-2811 ppm-years: RR=0.75, 95% CI=0.12-4.50; 2812+ ppm-years: RR=1.58, 95% CI=0.31-8.04), and there was no association with having worked as an autoclave cleaner (a job with potentially high exposure to VCM) (ever v. never autoclave: RR=1.08, 95% CI=0.40-2.92).

Each of three additional studies reporting observed and expected numbers of brain cancers found fewer than five observed or expected deaths: the German study (Weber et al., 1981), two observed and 1.3 expected; the Taiwanese study (Wong et al., 2002), two observed and 0.7 expected; and the study in the Soviet Union (Smulevich et al., 1988), four observed and 2.6 expected. None of these results was statistically significant.

The meta-analysis of Boffetta et al. (2003) reported a meta-SMR of 1.26 (95% CI=0.98-1.62) for brain cancer, based on data from the five independent cohort studies (Mundt et al., 2000; Ward et al., 2001; Weber et al., 1981; Wong et al., 2002; Smulevich et al., 1988). The relation between VCM and brain cancer is weak and is not statistically significant, an exposure-response relationship has not been demonstrated, and the results of the two most informative cohort studies (those in the US and Europe) are not confirmatory. None of the available studies mentions that any VCM-exposed subject had oligodendroglioma. Mortality records provided the diagnostic information for most of the occupational studies, and mortality data (death certificates) are not likely to provide a distinction among various subtypes of glioma, such as astrocytomas, glioblastomas, oligodendrogliomas or ependymomas.

This body of research does not support a conclusion that VCM causes brain cancer, or any particular form of primary malignant brain tumor, in humans. Numerous recent reviews of risk factors for brain cancer are consistent with this review in not identifying VCM exposure as an established cause of brain cancer.

Patricia A. Buffler, M.P.H., Ph.D.

26 January 2007
Date

REFERENCES

1. ATSDR. Agency for Toxic Substances and Disease Registry. Draft Toxicological Profile for Vinyl Chloride. US Department of Health and Human Services, September 2004.

2. Belli S, Bertazzi PA, Comba P, Foa V, Maltoni C, Masina A, Pirastu R, Reggiani A, Vigotti MA. A cohort study on vinyl chloride manufacturers in Italy: study design and preliminary results. Cancer Letters 1987;35:253-261.

3. Berry G, Rossiter CE. Vinyl chloride and mortality. Lancet 1976;ii:416-417.

4. Boffetta P, Matisan L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health 2003;29:220-229.

5. Bosetti C, La Vecchia C, Lipworth L, McLaughlin JK. Occupational exposure to vinyl chloride and cancer risk: a review of the epidemiologic literature. Eur J Cancer Prev 2003;12:427-430.

6. Buffler PA, Wood S, Eifler C, Suarez L, Kilian DJ. Mortality experience of workers in a vinyl chloride monomer production plant. J Occup Med 1979;21:195-203.

7. Byren D, Engholm G, Englund A, Westerholm P. Mortality and cancer morbidity in a group of Swedish VCM and PCV production workers. Environ Health Perspect 1976;17:167-170.

8. Cooper WC. Epidemiologic study of vinyl chloride workers: mortality through December 31, 1972. Environ Health Perspect 1981;41:101-106.

9. Doll R. Effects of exposure to vinyl chloride. An assessment of the evidence. Scand J Work Environ Health 1988;14:61-78.

10. Fox AJ, Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Brit J Ind Med 1977;34:1-10.

11. Hagmar L, Akesson B, Nielson J, Andersson C, Linden K, Attewell R, Moller T. Mortality and cancer morbidity in workers exposed to low levels of vinyl chloride monomer at a polyvinyl chloride processing plant. Am J Ind Med 1990;17:553-565.

12. Heldaas SS, Langard LS, Andersen A. Incidence of cancer among vinyl chloride and polyvinyl chloride workers. Br J Ind Med 1984;41:25-40

13. Heldaas SS, Andersen AA, Langard S. Incidence of cancer among vinyl chloride and polyvinyl chloride workers: further evidence for an association with malignant melanoma. Brit J Ind Med 1987;44:278-280.

14. Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the United States, 1977-2000. Cancer 2004:101:2293-2299.

15. Hill AB. The environment and disease: Association or causation? Proc Royal Soc Med 1965;48:295-300.

16. IARC. International Agency for Research on Cancer. Vinyl chloride. IARC monographs on the evaluation of carcinogenic risks to humans. Supplement 7. Lyons, France, 1987.

17. IARC. International Agency for Research on Cancer. IARC monographs on he evaluation of carcinogenic risks to humans: Preamble, 2006.

18. Infante PF. Observations of the site specific carcinogenicity of vinyl chloride to humans. Environ Health Perspect 1981;41:89.

19. Jones RD, Smith DM, Thomas PG. A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940-1974. Scand J Work Environ Health 1988;153-160.

20. Langard S, Rosenberg J, Andersen A, Heldaas SS. Incidence of cancer among workers exposed to vinyl chloride in polyvinyl chloride manufacture. Occup Environ Med 2000;57:65-68.

21. Laplanche A, Clavel-Chapelon F, Contassot J-C, Lanouziere C, French VCM Group. Exposure to vinyl chloride monomer: results of a cohort study after a seven year follow up. Brit J Ind Med 1992;49:134-137.

22. Lelbach WK. A 25-year follow-up study of heavily exposed vinyl chloride workers in Germany. Am J Ind Med 1996;29:446-458.

23. Lewis R, Rempala G, Dell LD, Mundt KA. Vinyl chloride and liver and brain cancer at a polymer production plant in Louisville, Kentucky. J Occup Environ Med 2003;45:533-537.

24. Lewis R, Rempala G. A case-cohort study of angiosarcoma of the liver and brain cancer at a polymer production plant. J Occup Environ Med 2003;45:538-545.

25. McLaughlin JK, Lipworth L. A critical review of the epidemiologic literature on health effects of occupational exposure to vinyl chloride. J Epidemiol Biostatistics 1999;4:253-275.

26. Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl chloride workers. Lancet 1974;2:397-398.

27. Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl chloride workers. Environ Health Perspect 1975;11:75-77.

28. Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of 10109 men in the North American vinyl chloride industry, 1942-72: update of cancer mortality to 31 December 1995. Occup Environ Med 2000;57:774-781.

29. Ott MG, Langner RR, Holder BB. Vinyl chloride exposure in a controlled industrial environment. Arch Environ Health 1975;30:333-339.

30. Nakamura K. A mortality study of vinyl chloride workers in Japan. JOEH 1983;5:49-57.

31. Price CM. (Letter) Vinyl chloride and U.S. EPA research. Environ Health Perspect 2005;113:A653-A654.

32. Simonato L, L'Abbe KA, Andersen A, Belli S, Comba P, Engholm G, Ferro G, Hagmar L, Langard S, Lundberg I, Pirastu R, Thomas P, Winkelmann R, Saracci R. A collaborative study of cancer incidence and mortality among vinyl chloride workers. Scand J Work Environ Health 1991;17:159-169.

33. Smulevich VB, Fedotova IV, Filatova VS. Increasing evidence of the rise of cancer in workers exposed to vinylchloride. Brit J Ind Med 1988;45:93-97.

34. Swaen GMH, Duijts SFA. Epidemiologic evidence for the carcinogenicity of vinyl chloride monomer. (Letter) Scand J Work Environ Health 2005;31:233-235.

35. Tabershaw IR, Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J Occup Med 1974;16:509-518.

36. Theriault G, Allard P. cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer. J Occup Med 1981;23:671-676.

37. Thun MJ and Sinks T. Understanding cancer clusters. CA Cancer J Clin 2004;54:273-280.

38. US EPA. Drinking water regulations and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water, 1994.

39. Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, De Santis M, Engholm G, Hagmar L, Langard S, Lundberg I, McElvenny D, Pirastu R, Sali D, Simonato L. Update of the follow-up of mortality and cancer incidence among

European workers employed in the vinyl chloride industry. Epidemiology 2001;12:710-718.

40. Waxweiler RJ, Springer W, Wagoner JK, Jones J. Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 1976;271:40-48.

41. Waxweiler RJ, Smith AH, Falk H, Tyroler HA. Excess lung cancer risk in a synthetic chemicals plant. Environ Health Perspect 1981;41:159-165.

42. Weber H, Reinl W, Greiser E. German investigations on morbidity and mortality of workers exposed to vinyl chloride. Environ Health Perspect 1981;41:95-99.

43. Wong O, Whorton MD, Foliart DE, Ragland D. An industry-wide epidemiologic study of vinyl chloride workers, 1942-1982. Am J Ind Med 1991;20:317-334.

44. Wong R-H, Chen P-C, Du C-L, Wang J-D, Cheng T-J. An increased standardized mortality ratio for liver cancer among polyvinyl chloride workers in Taiwan. Occup Environ Med 2002;59:405-409.

45. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-Oncology 2002;4:278-299.

46. Wu W, Steenland K, Brown D, Wells V, Jones J, Schulte P, Halperin W. Cohort and case-control analyses of workers exposed to vinyl chloride: an update. J Occup Med 1989;31:518-523.